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PATENT SPECIFICATION

NO DRAWINGS

Inventors: FRANK PETER DOYLE and JOHN HERBERT CHARLES NAYLER

920,300

Date of filing Complete Specification: Nov. 24, 1961.

Application Date: Nov. 25, 1960. *No. 40547/60.*

(Patent of Addition to No. 870,395 dated July 15, 1958 as improved upon or modified by No. 880,400 dated April 20, 1960),

Complete Specification Published: March 6, 1963.

Index at acceptance:—Class 2(3), AA(1C2A:1C2C:2C1).

International Classification:—C07d.

COMPLETE SPECIFICATION

Penicillins

ERRATUM

SPECIFICATION No. 920,300

Page 1, in the heading, *for* "(Patent of Addition to No. 870,395 dated July 15, 1958 as improved upon or modified by No. 880,400 dated April 20, 1960)." *read* "(Patent of Addition to No. 880,400 dated April 20, 1960)."

THE PATENT OFFICE

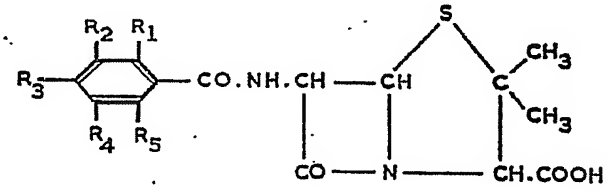
16th August 1963

aralkoxy, alkenyl, alkenyloxy, alkenylthio, mercapto, alkylthio, arylthio, aralkylthio, acyloxy, acylthio, acylamino, alkoxycarbonyl, alkylsulphonyl, dialkylamino, sulphamyl or nitro group, the substituents being the same or different and not more than four being hydrogen atoms, or any two adjacent substituents together completing an unsaturated carbocyclic ring system which may itself be sub-

[illegible] effective against resistant strains of bacteria.

We have now found that certain compounds of the general formula I wherein at least one of the substituents R_1, R_2, R_3, R_4 and R_5 is an amino group possess particularly desirable properties.

Accordingly, the present invention provides new penicillins of the general formula:



(II)

[*Price 4s. 6d.*]

BNSDOCID: <GB_____920300A__I_>

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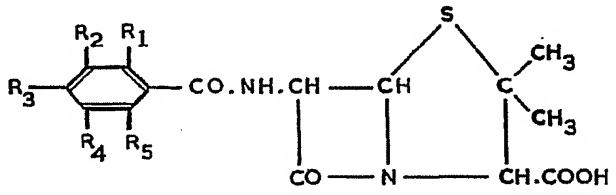
COMPLETE SPECIFICATION

Penicillins

We, BEECHAM RESEARCH LABORATORIES LIMITED, of Great West Road, Brentford, Middlesex, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new penicillins.

In our co-epnding Application No. 880,400 we have described and claimed new penicillins of the general formula:

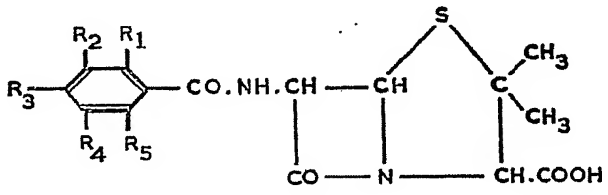


(I)

and non-toxic salts thereof, where R_1, R_2, R_3, R_4 and R_5 represent a hydrogen or halogen atom or an alkyl, aryl, acyl, aralkyl, cycloalkyl, heterocyclic, hydroxy, alkoxy, aryloxy, aralkoxy, alkenyl, alkenyloxy, alkenylthio, mercapto, alkylthio, arylthio, aralkylthio, acyloxy, acylthio, acylamino, alkoxycarbonyl, alkylsulphonyl, dialkylamino, sulphamyl or nitro group, the substituents being the same or different and not more than four being hydrogen atoms, or any two adjacent substituents together completing an unsaturated carbocyclic ring system which may itself be substituted. Some of these penicillins, in addition to their potent antibacterial activity, exhibit resistance to destruction by penicillinase and are thereby effective against resistant strains of bacteria.

We have now found that certain compounds of the general formula I wherein at least one of the substituents R_1, R_2, R_3, R_4 and R_5 is an amino group possess particularly desirable properties.

Accordingly, the present invention provides new penicillins of the general formula:



(II)

[*Price 4s. 6d.*]

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and non-toxic salts thereof, where R_1, R_2, R_3, R_4 and R_5 represent a halogen atom or an alkyl, aryl, acyl, aralkyl, cycloalkyl, heterocyclic, hydroxy, alkoxy, aryloxy, aralkoxy, alkenyl, alkenyloxy, alkenylthio, mercapto, alkylthio, arylthio, aralkylthio, acyloxy, acylthio, acylamino, alkoxycarbonyl, alkylsulphamyl, dialkylamino, sulphamyl, amino or nitro group or R_2, R_3, and R_4 represent a hydrogen atom, the substituents being the same or different and at least one being an amino group.

The salts are non-toxic salts including non-toxic metallic salts such as sodium, potassium, calcium and aluminium, ammonium and substituted ammonium salts, e.g. salts of such non-toxic amines as trialkylamines, including triethylamine, procaine, dibenzylamine, *N*-benzyl-beta-phenethylamine, 1 - ephenamine, N,N^1 - dibenzylethylenediamine, dehydroabietylamine, N,N^1 - bis - dehydroabietylethylenediamine, and other amines which have been used to form salts with benzylpenicillin.

The compounds of the present invention may be prepared and isolated in the manner described and claimed in our Application No. 880,400, the amino group or groups being protected in the conventional manner prior to formation of the acid chloride or its functional equivalent as an acylating agent.

The subsequent removal of the protecting group or groups to form the free amino-substituted penicillin can be effected by catalytic hydrogenation, e.g. with palladium or platinum on barium carbonate or on carbon. Suitable protecting groups are of the general formula $R^{11}—O—CO—$, wherein R^{11} is an alkyl, benzyl, substituted benzyl, phenyl, substituted phenyl or trityl group.

Alternatively, the compounds of the present invention may be prepared by forming the corresponding nitro, nitroso, or arylazo compound, which is then catalytically hydrogenated to form the amino derivative.

The following examples illustrate the invention.

EXAMPLE I

2-Methoxy-6-aminophenylpenicillin (sodium salt)

A mixture of 30% palladium/barium carbonate (5.26 g.) and water (80 ml.) was shaken under an atmospheric pressure of hydrogen for 2 hours (130 ml. of H_2 were absorbed). 2 - Methoxy - 6 - nitrophenylpenicillin (sodium salt) (5 g.) in water (100 ml.) was added and the hydrogenation continued at atmospheric pressure for 3 hours during which approximately 700 ml. of hydrogen were absorbed. The mixture was filtered free from catalyst and evaporated at low temperature and pressure to give the crude product as a greenish powder (4.1 g.); purity (by hydroxylamine assay) = 68%.

The product inhibited Staph. Oxford at a concentration of 0.6 mcg./ml., Staph 1 at 2.5 mcg./ml. and Staph. 2 at 2.5 mcg./ml.

EXAMPLE II

3-Amino-2,6-dimethoxyphenylpenicillin (sodium salt)

Method (a) 2,6-Dimethoxy-3-nitrophenylpenicillin (sodium salt) (5 g.) in water (100 ml.) was hydrogenated in the presence of 30% palladium/barium carbonate (5.26 g. suspended in 80 ml. water) by the general procedure of Example 1. The crude product was obtained as a greenish powder (4.33 g.); purity (by hydroxylamine assay) = 53%.

The product inhibited Staph. Oxford at a concentration of 1.25 mcg./ml., Staph. 1 at 2.5 mcg./ml., and Staph. 2 at 5 mcg./ml.

Method (b) Catalytic hydrogenation of 3-nitro-2,6-dimethoxybenzoic acid gave 3-amino-2,6-dimethoxybenzoic acid, which with benzyl chlorocarbonate and aqueous sodium hydroxide gave 3-(benzyloxycarbonylamino)-2,6-dimethoxybenzoic acid, m.p. 158—160° C. This acid (1.66 g.) and thionyl chloride (5 ml.) were mixed and warmed at 40° C. for 1 hour. Volatile material was removed by distillation *in vacuo*, then the residue was treated with dry chloroform (20 ml.) and re-evaporated to leave 3 - (benzyloxycarbonylamino) - 2,6 - dimethoxybenzoyl chloride as a light brown solid of sufficient purity for use in the next stage.

The acid chloride was dissolved in dry chloroform (20 ml.) and the solution was added dropwise during 20 minutes to a stirred mixture of chloroform (20 ml.), 6-aminopenicillanic acid (1.08 g.) and triethylamine (1.4 ml.). The mixture was stirred at room temperature for 80 minutes, then the resulting solution was transferred to a separating funnel and washed with 0.3 N. hydrochloric acid (16 ml.) followed by water (2 × 20 ml.). The chloroform solution was then neutralised by shaking with the calculated quantity of 3% aqueous sodium bicarbonate (14 ml.) and the resulting emulsion was evaporated at low temperature and pressure to leave a light brown solid, which was finally dried in a vacuum desiccator. This sodium salt of 3 - (benzyloxycarbonylamino) - 2,6 - dimethoxyphenylpenicillin (2.32 g.) was estimated by colorimetric assay with hydroxylamine to be about 66% pure.

A portion (1 g.) of this product was dissolved in water and hydrogenated over a palladium/barium carbonate catalyst (1.05 g. of 30%) as described in Example 1. The catalyst was then removed by filtration and the aqueous filtrate and washings were evaporated at low temperature and pressure. The residual sodium salt of 3 - amino - 2,6-dimethoxyphenylpenicillin was finally dried in a vacuum desiccator to give a buff powder (0.62 g.), which was estimated by colorimetric assay with hydroxylamine to be about 65% pure.

When subjected to paper chromatography

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using the solvent system butanol-ethanol-water (4:1:5, top layer) the product gave a single zone of antibacterial activity having R_F 0.17. Under the same conditions 3 - (benzyloxycarbonylamino) - 2,6 - dimethoxyphenylpenicillin had R_F 0.5.

Method (c) 2,6-Dihydroxy-3-phenylazobenzoic acid (Gore *et al., Proc. Indian Acad. Sci.*, 1949, *29A*, 289) was treated with dimethyl sulphate and potassium carbonate in acetone to give methyl 2,6-dimethoxy-3-phenylazobenzoate, m.p. 110° C., which on alkaline hydrolysis afforded the orange-red 2,6-dimethoxy-3-phenylazobenzoic acid, m.p. 214—215° C. This acid (2.8 g.) and thionyl chloride (2.9 ml.) were heated together at 90 to 100° C. for 1 hour to give a clear solution, which was then evaporated *in vacuo*. Treatment of the residue with dry chloroform (10 ml.), followed by re-evaporation *in vacuo*, gave 2,6 - dimethoxy - 3 - phenylazobenzoyl chloride of sufficient purity for use in the next stage.

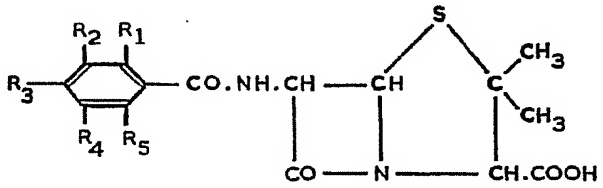
The acid chloride was dissolved in dry chloroform (20 ml.) and added dropwise during 15 minutes to a stirred mixture of chloroform (30 ml.), 6-amino-penicillanic acid (2.16 g.) and triethylamine (2.8 ml.). The mixture was stirred at room temperature for 1 hour, then the resulting clear solution was transferred to a separatory funnel and washed with 0.5 N. hydrochloric acid (20 ml.) followed by water (20 ml.). The chloroform phase was then neutralised by shaking with the calculated quantity of 3% aqueous sodium bicarbonate solution (28 ml.) and the resulting emulsion was evaporated at low temperature and pressure to leave an orange solid, which was finally dried in a vacuum desiccator. This sodium salt of 2,6-dimethoxy-3-phenylazophenylpenicillin (4.35 g.) was estimated by colorimetric assay with hydroxylamine to be about 58% pure.

A portion (1 g.) of this product was dissolved in water (20 ml.) and hydrogenated over a palladium/barium carbonate catalyst (1.05 g. of 30%), as described in Example I. The catalyst was then removed by filtration and the aqueous filtrate and washings were extracted with ether to remove aniline, then evaporated at low temperature and pressure. The residual sodium salt of 3-amino-2,6-dimethoxyphenylpenicillin was finally dried in a vacuum desiccator to give a buff powder (0.61 g.) which was estimated by colorimetric assay with hydroxylamine to be about 43% pure.

Paper chromatography in butanol-ethanol-water (4:1:5, top layer) indicated the main biologically active component to be 3-amino-2,6-dimethoxyphenylpenicillin (R_F 0.18), although a trace of unreduced 2,6-dimethoxy-3-phenylazophenylpenicillin (R_F 0.51) was still present.

WHAT WE CLAIM IS:—

1. New penicillins of the general formula:



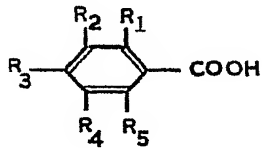
(II)

and non-toxic salts thereof, where R_1, R_2, R_3, R_4 and R_5 represent a halogen atom or an alkyl, aryl, acyl, aralkyl, cycloalkyl, heterocyclic, hydroxy, alkoxy, aryloxy, aralkoxy, alkenyl, alkenyloxy, alkenylthio, mercapto, alkylthio, arylthio, aralkylthio, acyloxy, acylthio, acylamino, alkoxycarbonyl, alkylsulphamyl, dialkylamino, sulphamyl, amino or nitro group or R_2, R_3, and R_4 represent a hydrogen atom, the substituents being the same or different and at least one being an amino group.

2. 2 - Methoxy - 6 - aminophenylpenicillin and its non-toxic salts.

3. 3 - Amino - 2,6 - dimethoxyphenylpenicillin and its non-toxic salts.

4. A process for the preparation of the new penicillins and non-toxic salts thereof claimed in claim 1, wherein 6-aminopenicillanic acid, or a neutral salt thereof, is reacted with an acid chloride, bromide, anhydride or mixed anhydride derived from a carboxylic acid of the general formula:



wherein R_1, R_2, R_3, R_4 and R_5 are as defined in claim 1, in which the amino group or groups are protected, and thereafter the protecting group or groups are removed under conditions sufficiently mild to avoid destruction of the penicillin nucleus.

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5. A process as claimed in claim 4, wherein the amino group or groups are protected with a group of the formula R^{11}—O—CO—, in which R^{11} is alkyl, benzyl, substituted benzyl, phenyl, substituted phenyl or trityl.

6. A process as claimed in claim 5, wherein the removal of the protecting group or groups is effected by catalytic hydrogenation.

7. A process for the preparation of the new penicillins and non-toxic salts thereof claimed in claim 1, wherein a corresponding nitro, nitroso or arylazo penicillin is catalytically hydrogenated to form the amino derivative.

8. A process as claimed in claim 6 or claim 7, wherein the catalyst used is palladium or platinum supported on barium carbonate or carbon.

9. A process for the preparation of the penicillins and non-toxic salts thereof claimed in claim 1 substantially as described with reference to either of the specific Examples.

10. Penicillins and non-toxic salts thereof claimed in claim 1 when prepared by a process as claimed in any one of claims 4 to 9.

RONALD SMITHER,
Agent for the Applicants,
Chartered Patent Agent.

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